

## COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF LIPID REGULATING AGENTS

### FIELD OF THE INVENTION

[0001] The present invention relates to drug delivery systems, and in particular to pharmaceutical compositions for the improved delivery of hydrophobic compounds.

### BACKGROUND

[0002] Hydrophobic therapeutic agents, i.e., therapeutic compounds having poor solubility in aqueous solution, present difficult problems in formulating such compounds for effective administration to patients. A well-designed formulation must, at a minimum, be capable of presenting a therapeutically effective amount of the hydrophobic compound to the desired absorption site, in an absorbable form. Even this minimal functionality is difficult to achieve when delivery of the hydrophobic therapeutic agent requires interaction with aqueous physiological environments, such as gastric fluids and intestinal fluids. Pharmaceutical compositions for delivery of such hydrophobic therapeutic agents must carry the hydrophobic compound through the aqueous environment, while maintaining the hydrophobic compound in an absorbable form, and avoiding the use of physiologically harmful solvents or excipients.

[0003] A number of approaches to formulating hydrophobic therapeutic agents for oral or parenteral delivery are known. One well-known approach uses surfactant micelles to solubilize and transport the therapeutic agent. Micelles are agglomerates of colloidal dimensions formed by amphiphilic compounds under certain conditions. Micelles, and pharmaceutical compositions containing micelles, have been extensively studied and are described in detail in the literature; see, e.g., Remington's Pharmaceutical Sciences, 17<sup>th</sup> ed. (1985), the disclosure of which is incorporated herein in its entirety. In aqueous solution, micelles can incorporate hydrophobic therapeutic agents in the hydrocarbon core of the micelle, or entangled at various positions within the micelle walls. Although micellar formulations can solubilize a variety of hydrophobic therapeutic agents, the loading capacity of conventional micelle formulations is limited by the solubility of the therapeutic agent in the micelle surfactant. For many hydrophobic therapeutic agents, such solubility is too low to offer formulations that can deliver therapeutically effective doses.

[0004] Another conventional approach takes advantage of the increased solubility of hydrophobic therapeutic agents in oils (triglycerides). Hydrophobic therapeutic agents, while poorly soluble in aqueous solution, could be sufficiently lipophilic that therapeutically effective concentrations of the therapeutic agents can be prepared in triglyceride-based solvents. Thus, one conventional approach is to solubilize a hydrophobic therapeutic agent in a bioacceptable triglyceride solvent, such as a digestible vegetable oil, and disperse this oil phase in an aqueous solution. The dispersion may be stabilized by emulsifying agents and provided in emulsion form. Alternatively, the therapeutic agent can be provided in a water-free formulation, with an aqueous dispersion being formed in the in vivo gastrointestinal environment. The properties of these oil-based formulations are determined by such factors as the size of the triglyceride/therapeutic agent colloidal particles and the presence or absence of surfactant additives.

[0005] In simplest form, a triglyceride-containing formulation suitable for delivering hydrophobic therapeutic agents through an aqueous environment is an oil-in-water emulsion. Such emulsions contain the hydrophobic therapeutic agent solubilized in an oil phase which is dispersed in an aqueous environment with the aid of a surfactant. The surfactant may be present in the oil-based formulation itself, or may be a compound provided in the gastrointestinal system, such as bile salts, which are known to be in vivo emulsifying agents. The colloidal oil particles sizes are relatively large, ranging from several hundred nanometers to several microns in diameter, in a broad particle size distribution. Since the particle sizes are on the order of or greater than the wavelength range of visible light, such emulsions, when prepared in an emulsion dosage form, are visibly "cloudy" or "milky" to the naked eye.

[0006] Although triglyceride-based pharmaceutical compositions are useful in solubilizing and delivering some hydrophobic therapeutic agents, such compositions are subject to a number of significant limitations and disadvantages. Emulsions are thermodynamically unstable, and colloidal emulsion particles will spontaneously agglomerate, eventually leading to complete phase separation. The tendency to agglomerate and phase separate presents problems of storage and handling, and increases the likelihood that pharmaceutical emulsions initially properly prepared will be in a less optimal, less effective, and poorly-characterized state upon ultimate administration to a patient. Uncharacterized degradation is particularly disadvantageous, since increased particle size slows the rate of transport of the colloidal particle and digestion of the oil component, and hence the rate and extent of absorption of the therapeutic agent. These problems lead to poorly-characterized and potentially harmful changes in the effective dosage received by the patient. Moreover, changes in colloidal emulsion particle size are also believed to render absorption more sensitive to and dependent upon conditions in the gastrointestinal tract, such as pH, enzyme activity, bile components, and stomach contents. Such uncertainty in the rate and extent of ultimate absorption of the therapeutic agent severely compromises the medical professional's ability to safely administer therapeutically effective dosages.

[0007] A further disadvantage of triglyceride-containing compositions is the dependence of therapeutic agent absorption on the rate and extent of lipolysis. Although colloidal emulsion particles can transport hydrophobic therapeutic agents through the aqueous environment of the gastrointestinal tract, ultimately the triglyceride must be digested and the therapeutic agent must be released in order to be absorbed through the intestinal mucosa. The triglyceride carrier is emulsified by bile salts and hydrolyzed, primarily by pancreatic lipase. The rate and extent of lipolysis, however, are dependent upon several factors that are difficult to adequately control. For example, the amount and rate of bile salt secretion affect the lipolysis of the triglycerides, and the bile salt secretion can vary with stomach contents, with metabolic abnormalities, and with functional changes of the liver, bile ducts, gall bladder and intestine. Lipase availability in patients with decreased pancreatic secretory function, such as cystic fibrosis or chronic pancreatitis, may be undesirably low, resulting in a slow and incomplete triglyceride lipolysis. The activity of lipase is pH dependent, with deactivation occurring at about pH 3, so that the lipolysis rate will vary with stomach contents, and may be insufficient